Mitochondrial Disease

BIOMARKERS

Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society

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There are published diagnostic guidelines

Genetics in Medicine, 2015
Available online at bit.ly/mitoconsensus

When Mitochondria Disease is Suspected

START WITH TESTING BIOMARKERS IN BLOOD AND URINE

Mitochondrial Biomarkers Are Imperfect

THEY HAVE IMPERFECT SENSITIVITY AND SPECIFICITY

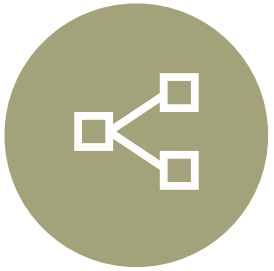
Pathophysiology

When mitochondria are unhealthy there is an accumulation of NADH as well as other metabolic perturbations

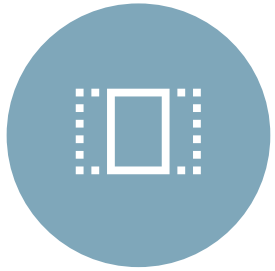
This leads to changes in normal metabolism of lactic acid, certain amino acids, organic acids and fatty acids

Abnormalities of Mitochondrial Function Can Be Seen in Measurements of

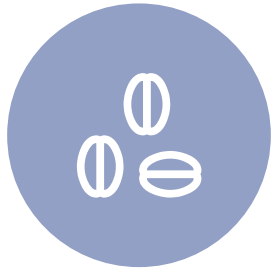
LACTATE AND PYRUVATE IN BLOOD AND CSF



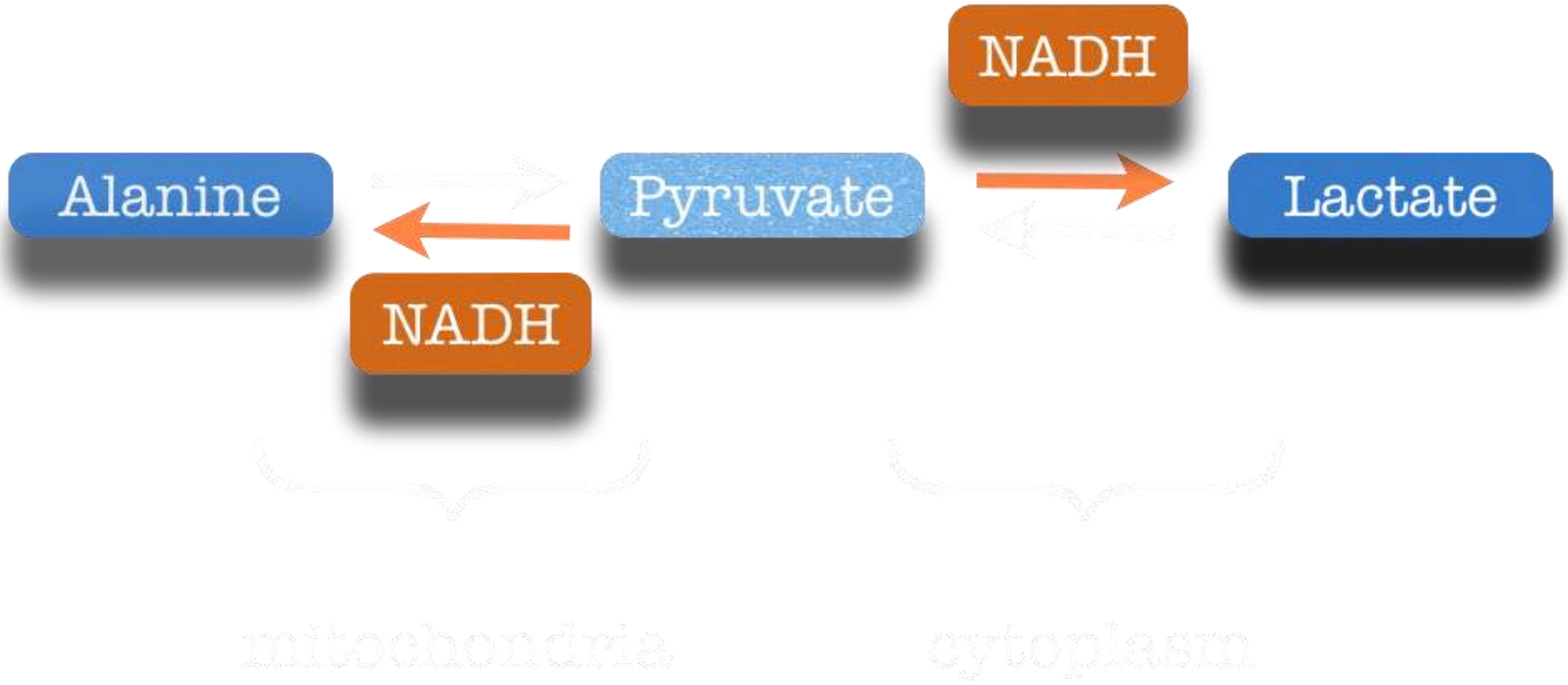
AMINO ACIDS, IN PLASMA AND CSF



ACYLCARNITINES, IN PLASMA



ORGANIC ACIDS, IN URINE



Pyruvate can be Converted to Lactate or Alanine

With mitochondrial dysfunction, this pathway moves primarily in one direction

Lactic acid may accumulate in the blood or CSF

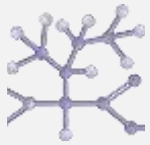
Alanine, measured in amino acids, may also accumulate

Lactic Acid can be elevated for multiple non mitochondrial disease reasons

- Difficulty with specimen collection (not free-flowing blood) or erroneous specimen handling (not put on ice)
- Anaerobic Exercise
- Sepsis or Hypoxia
- Cardiac or Renal Failure
- Medication/Toxin effects
- Malignancy
- Other Biochemical Genetic Diseases

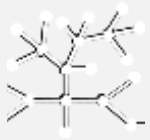
There are several amino acids that may accumulate in addition to alanine

Alanine



Glycine

Proline



Lysine

Amino Acids are Catabolized to Organic Acids

Elevated Organic Acids Include

- Malate
- Fumarate
- 3-methyl-glutaconic Acid
- Dicarboxylic Acid, 2-Oxoadipic and 2-Aminoadipic Acid
- Methylmalonic Acid
- Other Citric Acid Cycle Intermediates (less specific)
- Lactate (less specific)

Fatty Acids are Metabolized via the Carnitine Shuttle

Acylcarnitine profiles can help assess perturbations in Fatty Acid metabolism

Fatty Acid metabolism may be disrupted with mitochondrial dysfunction and seen on this testing in blood

Imperfect Sensitivity and Specificity

These biomarkers lack great sensitivity and specificity

A full differential diagnosis is needed for the patient's symptoms

If there is a high degree of suspicion for primary mitochondrial disease – an evaluation by a mitochondrial specialist for genetic testing may be indicated